

WHAT IS CLAIMED IS:

1. A method of inhibiting CD28 pathway activation associated with an increase in cellular production of a T_HCD28 lymphokine in a T cell population, wherein activation occurs by the binding of a stimulatory CD28 ligand to a CD28 receptor stimulatory binding site, the method comprising the steps of:
 - 5 a) selecting an inhibitory ligand capable of binding to the stimulatory CD28 ligand;
 - b) providing the inhibitory ligand in a biologically compatible form; and
 - c) administering the inhibitory ligand to the population in an amount sufficient to bind and inhibit the stimulatory ligand from binding the CD28 receptor stimulatory binding site.
- 15 2. The method of Claim 1, wherein the stimulatory ligand comprises a natural CD28 ligand.
3. The method of Claim 1, wherein the inhibitory ligand comprises an antibody or fragment thereof to the stimulatory ligand.
- 20 4. The method of Claim 1, wherein the inhibitory ligand comprises a soluble form of CTLA-4.
5. The method of Claim 4, wherein the ligand comprises CTLA-4Ig.
- 25 6. The method of Claim 1, wherein the inhibitory ligand is of synthetic origin.
7. The method of Claim 1, wherein the inhibitory ligand comprises a recombinant molecule.
- 30 8. The method of Claim 1, further comprising the step of:
 - d) administering a second inhibitory ligand capable of binding but not stimulating the CD28 receptor binding site.

9. A method of suppressing the production of a T_HCD28 lymphokine by a population of T cells, the method comprising the steps of:

- a) administering an inhibitory ligand which binds a stimulatory ligand for CD28;
- 5 b) providing the ligand in biologically compatible form; and
- c) administering the provided ligand in an amount sufficient to suppress production of the lymphokine in the population.

10. The method of Claim 9, wherein the inhibitory ligand comprises a soluble form of CTLA-4.

11. The method of Claim 10, wherein the inhibitory ligand comprises CTLA-4Ig.

15 12. The method of Claim 9, wherein the T cell population is in a patient in an autoimmune state.

13. A method of suppressing T_HCD28 lymphokine production in a patient having a population of T cells, the method comprising the steps of:

- 5 a) providing an inhibitory ligand which binds a natural stimulatory ligand for CD28; and
- b) administering the inhibitory ligand in a therapeutically effective amount to the population of T cells.

14. The method of Claim 13, wherein the administration of the ligand
10 to the population of T cells is *in vivo*.

15. The method of Claim 13, wherein the administration of the ligand to the population of T cells is *in vitro*, and further comprising the step of:

- 15 d) introducing the population of T cells into the patient after administration.

16. The method of Claim 15, wherein the T cell population is removed from the patient prior to ligand administration.

20 17. The method of Claim 13, wherein the inhibitory ligand comprises a soluble form of CTLA-4.

18. The method of Claim 17, wherein the inhibitory ligand comprises CTLA-4Ig.

19. A method of treating an autoimmune disease in a patient comprising the steps of:

a) selecting an inhibitory ligand which binds a natural stimulatory ligand to CD28; and

5 b) administering a therapeutically effective amount of the ligand to the patient.

20. The method of Claim 19, wherein the stimulatory ligand is B7 and the inhibitory ligand comprises a soluble form of CTLA-4.

10 21. The method of Claim 19, wherein the inhibitory ligand comprises CTLA-4Ig.

22. The method of Claim 20, wherein the administration is *in vivo*.

15 23. The method of Claim 20, wherein the administration is *in vitro* to a population of cells removed from the patient, and further comprising the step of:
c) reintroducing the cells to the patient after administration.

20 24. The method of Claim 20, wherein the autoimmune disease is multiple sclerosis.

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